

Serial No. 07/943,246

R E M A R K S

This communication is responsive to the Office Action mailed in the above-captioned application on July 22, 1993. Claims 1-15 originally were submitted and are presented for examination. Reconsideration and reexamination of the application in light of the amendments and the remarks herein set forth is respectfully requested.

PROVISIONAL REJECTION FOR OBVIOUSNESS-TYPE DOUBLE-PATENTING

The provisional rejection for obviousness-type double-patenting of claims 1-15 over claims 1-35 in co-pending U.S. application serial number 07/636,995 ("'995 application") is traversed for the reasons set forth below.<sup>1</sup>

The rejection admits that none of the rejected claims is identical to any of claims 1-35 in the '995 application. It is stated, however, that "[T]he claims of the instant application are obvious over the claims of the '995 application as the genomic sequence for protein C is a DNA sequence having protein C activity."

The claims presented below are representative of the rejected claims and those in the '995 application, as to this rejection. To facilitate comparison, some differences between the two sets of claims have been highlighted.

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<sup>1</sup> It is noted that the '995 application is characterized incorrectly in the rejection as "U.S. Patent No. 07/638,995, an apparent typographical error."

**This Application**

1. A transgenic non-human mammal containing an exogenous DNA sequence stably integrated in its genome, wherein said exogenous DNA sequence comprises substantially the 5' 4.2 kb Sau3A - Kpn1 promoter of the mouse whey acidic protein gene, or a variant thereof, operably linked to a DNA sequence encoding a polypeptide having protein C activity and a signal peptide, wherein said whey acidic protein promoter is specifically active in mammary cells and said signal peptide is effective in directing the secretion of said polypeptide into the milk of said transgenic mammal.

**'995 Application**

1. A transgenic non-human mammal containing an exogenous DNA sequence stably integrated in its genome, wherein said exogenous DNA sequence comprises a promoter operably linked to a DNA sequence encoding a polypeptide having protein C activity and a signal peptide, said promoter is specifically active in mammary cells and said signal peptide is effective in directing the secretion of said protein C into the milk of said transgenic mammal, wherein said polypeptide is secreted into the milk of said transgenic non-human mammal and has high specific activity determined by a conventional assay of protein C activity.

It is respectfully submitted that any rejection for obviousness double-patenting of claim 1 in the present application over claim 1 of the '995 application must assert that a transgenic animal, as claimed, containing an exogenous DNA sequence that comprises "substantially the 5' 4.2 kb Sau3A - Kpn1 promoter of the mouse whey acidic protein gene, or a variant thereof, operably linked to a DNA sequence encoding a polypeptide having protein C activity" would have been obvious over a transgenic non-human mammal, as claimed in the '995 application, containing an exogenous DNA sequence that comprises a promoter operably linked to a DNA sequence encoding a polypeptide having protein C activity."

If the rejection had been made more particularly over dependent claim 4 in the '995 application which recites, "wherein said promoter is a whey acidic protein promoter," it would have been necessary to set forth a reasoned assertion that transgenic animals that express protein C by the "the 5' 4.2 kb Sau3A - Kpn1 promoter of the mouse whey acidic protein gene" would have been obvious over transgenic that express protein C by "a whey acidic protein promoter."

As set forth in EXAMPLE 11 of the present disclosure, for example, the use of the claimed 4.2 kb long WAP promoter has been found to provide "unexpected" results compared to other WAP promoters.<sup>2</sup> Expression of protein C using the long promoter in transgenics, as set forth in the example, exhibits higher milk concentrations and improved mammary tissue specificity.

The rejection does not address the foregoing differences between the claimed invention in this application and the invention recited in the claims of the '995 application. Thus, the office action fails to set forth proper grounds for the rejection which, accordingly, is improper and should be withdrawn.

It is noted briefly that dependent claims in the present application recite WAP promoter fragments and protein C encoding DNAs with greater particularity than mentioned above. The rejection improperly ignores these more particular recitations.

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<sup>2</sup> This point is discussed in greater detail below in the remarks on the rejections under Section 103 beginning on page 21.

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The unobviousness of the claimed invention over the invention claimed in the '995 application is set forth further in discussing the rejections under Section 103 below.

**PROVISIONAL REJECTION FOR OBVIOUSNESS**

Claims 1-15 provisionally have been rejected for obviousness over the '995 application cited in the foregoing rejection for obviousness-type double-patenting. The grounds of this rejection, though based on the disclosure of the '995 rather than the claims, are the same as for the foregoing rejection.

The rejection suffers from the deficiency discussed above: failing to set out a proper *prima facie* case that a transgenic mammal expressing protein C in its milk by the activity of "the 5' 4.2 kb *Sau3A* - *Kpn1* promoter of the mouse whey acidic protein gene" would have been obvious over similar transgenic animals in which the mammary gland specific promoter is "a promoter" or a "whey acidic protein promoter."

It will be appreciated that a genus, disclosed or claimed, does not anticipate and does not, *per se*, render obvious any subgenus or species which it contains. To the contrary, a species or subgenus generally is anticipated only by prior disclosure of the identical species or subgenus, not anything different. Likewise, the unobviousness of a species or subgenus over a previously disclosed genus must be determined in accordance with Section 103. Analysis of unobviousness therefore must address the question of whether the claimed species or

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subgenus would have been obvious to those of ordinary skill in the art in view of the genus.

The present rejection does not assert that the genus of transgenic animals disclosed in the '995 application would have rendered obvious the transgenic animals containing the specific subgenus and species of DNAs recited in the rejected claims. It therefore is urged, respectfully, that the rejection is improper and should be withdrawn.

The unobviousness of the claimed invention over the invention disclosed and claimed in the '995 application is discussed further under Section 103 below.

**REJECTIONS UNDER 35 U.S.C. §101**

The rejection under Section 101 has been obviated by amending claim 11 to recite "non-human mammal."

Further in this regard, however, it is noted that search of Chapter 35 of the U.S. Code, Chapter 37 of the Code of Federal Rules, and published administrative and judicial decisions bearing on patents failed to uncover authority for the assertion that "a method of producing transgenic animals, which includes humans" is not statutory subject matter under Section 101. Therefore, a supporting citation is requested.

**REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH**

Each of the rejections under Section 112, first paragraph is discussed individually below.

**I. WRITTEN DESCRIPTION**

Claims 1-15 are rejected "as failing to provide an adequate written description," following the restatement of Section 112 on page 4 of the Office Action. No alleged inadequacy in the written description is set forth in the rejection, however, which appears to be directed exclusively to enablement issues. All of the enablement issues are addressed in the following section of this response. Insofar as the rejection was predicated on grounds that the written description is inadequate, an explanation specifically pointing out the alleged deficiencies is requested.

**II. ENABLEMENT**

The starting point for rejection on enablement grounds long has been taken from the decision of the CCPA in *In re Marzocchi*:

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enablement requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exit, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. (Original emphasis italicized, other emphasis added. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971)).

It is respectfully submitted that the present rejection does not set forth reasons to doubt the objective truth of the disclosure that the DNAs for

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practicing the claimed invention readily can be obtained by those of skill in the art or that the claimed invention can be practiced in mammals generally, as discussed in greater detail below.

1. DNAs of the claimed invention can be obtained without undue experimentation from well known and readily available starting materials

The rejection asserts that "Applicant has not indicated a reproducible and publicly available source" of DNAs containing the 4.2kb WAP promoter fragment and DNAs encoding protein C. It further asserts that the named plasmids in the disclosure must be deposited to meet the enablement requirement of Section 112.

Enablement allegedly is inadequate for DNAs which comprise "substantially the 5' 4.2 kb *Sau3A* - *Kpn1* promoter of the mouse whey acidic protein gene, or a variant thereof, operably linked to a DNA sequence encoding a polypeptide having protein C activity."

It is respectfully submitted that starting materials to make the aforementioned DNAs are well known and readily available. Those of skill in the art can use these starting materials to make DNAs in accordance with the disclosure and claimed invention without undue experimentation by a variety of conventional methods. Thus, applicants' source of DNAs is irrelevant in this regard. Moreover, it is respectfully submitted that recombinant DNA techniques are quite robust and reliable and there is no basis for the assertion that other cloned DNAs of the same type will differ from those specifically employed by applicant, necessitating deposit. Each of these points is discussed in greater detail below.

**Protein C encoding DNAs are well known and readily available**

The examiner objects to the specification because it indicates that the protein C DNA of certain embodiments of the invention was obtained from an individual and may not be publicly available.

A plasmid containing the DNA for human protein C is available to the public through the National Regional Research Laboratory (Accession number NRRL B-15926), as set forth in Bang et al.'s U.S. Patent No. 4,775,642 at column 9, lines 36 to 45.<sup>3</sup>

In addition, the amino acid and DNA sequences of protein C have been published and are known to those of skilled in the art, as set forth in the present disclosure and in documents submitted in the Information Disclosure Statement entered in the application on December 31, 1992. For instance, Forster et al., *P.N.A.S.* 82: 4673 (1985), U. S. patent No. 4,775,624 to Bang et al.<sup>4</sup> and U. S. Patent No. 4,992,373<sup>5</sup> all describe the cDNA or genomic sequence of human protein C. Furthermore, U. S. Patent Nos. 4,968,626 to Forster et al. and 4,959,318 to Forster et

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<sup>3</sup> Reference A1 in the I.D.S. submitted in the application on February 14, 1992.

<sup>4</sup> Both referred to in the present specification on page three.

<sup>5</sup> Document A2 in the Information Disclosure Statement of December 31, 1992.



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al., and Pultzky (1986) also describe protein C sequences.<sup>6</sup>

It is respectfully maintained that these known and readily available protein C sequences enable one of ordinary skill to obtain without undue experimentation any protein C encoding DNAs necessary or useful in the presently claimed invention.

The techniques for reisolating cDNAs and genomic clones using probes based on nucleic acid or amino acid sequences are well known and routine to those of skill in the art. Since the references teach sources and probe sequences successful in isolating protein C DNAs, it cannot be maintained that those of skill, well familiar with cDNA and genomic cloning, will require undue experimentation to obtain protein C encoding DNAs. To the contrary, the skilled artisan can make and screen libraries to obtain the DNAs without undue experimentation. In fact, suitable libraries and probes can be purchased from commercial sources and the DNAs may even be obtained by contracting with commercially available services.

Thus, protein C encoding DNA is available and can be made from readily available starting materials by routine effects.

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<sup>6</sup> Copies of U.S. Patent Nos. 4,968,626 and 4,959,310 and Pultzky (1986) are appended hereto as EXHIBITS 1, 2 and 3, respectively.

**WAP promoter DNAs are well known and readily available**

A plasmid containing the entire murine WAP gene has been deposited in the American Type Culture Collection (ATCC No. 63005).<sup>7</sup> The DNA was deposited by Dr. Hennighausen, who provided the WAP encoding DNA used in the present invention, as noted in the specification. Furthermore, sequences of the murine WAP gene have been published by Campbell (1984), as set forth in specification, and are known to those of skill in the art.<sup>8</sup> The sequences will enable the skilled artisan to obtain murine WAP DNAs in accordance with the claimed invention, as set forth above regarding protein C.

Accordingly, it is respectfully maintained that all the DNA starting materials necessary to make DNAs suitable for use in the claimed invention are known and readily available. Specifically, WAP DNAs suitable for use in the claimed invention are known and readily available and protein C-encoding DNAs suitable for use in the claimed invention are known and readily available.

**The disclosure will enable those of skill to make DNAs of the claimed invention from known and readily available WAP promoter and protein C DNAs by entirely routine procedures**

The disclosure provides explicit guidance for those of skill in the art to use the aforementioned

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<sup>7</sup> A copy of the relevant ATCC listing is attached hereto as EXHIBIT 4.

<sup>8</sup> This reference was cited by the examiner in rejection claims under Section 103.

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starting materials to make DNAs in accordance with the claimed invention without undue experimentation.

Techniques for constructing DNAs from such starting materials to place a structural gene under the control of a heterologous promoter are practiced ubiquitously by those of skill in the art, routinely.

For instance, the skilled artisan, starting from well known and readily available protein C and WAP DNAs, such as those disclosed in the application and those described above, will be enabled by the disclosure to make and use DNAs the same as WAPpC1 and WAPpC2. The structure of these plasmids is set forth in detail in the disclosure. The disclosed restriction maps of these plasmids, for instance, clearly indicates the enzymes to use to obtain the WAP promoter and protein C DNAs in WAPpC1 and WAPpC2, and how to ligate them together to make the plasmids. The constructions are simple. The necessary assembly techniques are among the most basic techniques in the art. Accordingly, making the constructs would be routine.

The same is true for DNAs of the claimed invention in which the long 4.2 kb WAP promoter is used to direct expression of a protein C gene, rather than the short promoter in WAPpC1 and WAPpC2. The WAP gene and the 4.2 kb promoter fragment are amply described in the specification. The disclosed restriction sites uniquely define the fragment in WAP genomic DNA. A fragment defined by restriction sites is an empirically observable fact. Those of skill need only carry out a restriction digestion, resolve the products by gel electrophoresis and

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stain and illuminate the result gel to determine the fragment. All the procedures are simple, ubiquitous techniques practiced habitually in the art.

In sum, it is respectfully submitted that the disclosure will enable those of skill in the art to make and use DNAs in accordance with the claimed invention without undue efforts without the deposit allegedly required. It is respectfully submitted, therefore, that the depository requirement should be withdrawn.

It is believed that the foregoing comments fairly represent the level of ordinary skill in the art, the state of the art and the routine experimentation required to make DNAs in accordance with the claimed invention. If the requirement is maintained despite the foregoing remarks, therefore, further explanation is respectfully requested. In particular, it is respectfully requested that the rejection indicate specifically the procedures or techniques that would necessitate undue experimentation that would be avoided by the required deposit.

2. THE DISCLOSURE WILL ENABLE THOSE SKILLED IN THE ART TO MAKE A VARIETY OF TRANSGENIC MAMMALS WHICH EXPRESS PROTEIN C IN THEIR MILK

The rejection alleges that "the production of transgenic animals which exhibit tissue specific production of a specific protein is unpredictable." The rejection further alleges, apparently in this regard, that, "Applicant has not taught nor provided evidence that protein C DNA sequences will integrate into the genome of all mammals and that [this] will permit the production of heterologous protein C in the milk of all mammals." The rejection is traversed for the reasons set forth below.

It is submitted that the rejection errs in asserting that Section 112 requires "applicant" to show "protein C DNA sequences will integrate into genomes of all mammals."<sup>9</sup> First, it is noted that the burden initially is on the Patent Office to set forth reasons to doubt the objective truth of applicants' assertion that WAP/protein C DNAs of the claimed invention generally will integrate into the genomes of mammals.<sup>10</sup>

The integration of DNA into host cell genomes following microinjection, among other techniques, has been observed universally in vitro and in vivo in cells and organisms used experimentally in this regard. DNA integration is the basis for reliable techniques practiced in a variety of plants and insects as well as mice, rats, pigs, sheep, goats and cows, among others. The examiner has advanced no rational basis for the assertion that the DNAs of the claimed invention will be different from other DNAs in this regard. This ground of rejection is improper.

The assertion that applicant must provide evidence in "all" mammals to enable a claim that recites "mammals" also is wrong. It is well established a single exemplified species can enable a genus. Ordinarily, exemplification of, at most a few species is sufficient. And it never has been held that all species must be exemplified to enable a genus. Indeed, it is a basic principle that claims may embrace some inoperative embodiments, which clearly indicates it never is necessary

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<sup>9</sup> Emphasis added.

<sup>10</sup> As set forth in *In re Marzocchi, supra*.

to demonstrate operativity for every embodiment of a claimed invention.<sup>11</sup> As a matter of law, therefore, it is submitted that the asserted necessity to provide evidence of integration or protein C production in "all" mammals is improper.

It also is submitted that the assertion that a protein C-encoding DNA may integrate into a critical sequence in the genome of an injected embryo, however true it may be, does not show that the disclosure is not enabling. Any DNA injected into an embryo poses the same risk as the claimed DNAs. Moreover, the same risk is posed in the injected embryo of all mammals, not just mice. Inasmuch as the assertion applies to any gene and any mammal with as much validity as to the claimed invention it is directly contrary to the manifest success in the art of making transgenic mammals.<sup>12</sup> This ground of the rejection is improper and should be withdrawn.

The allegation that "[T]he mouse whey acid protein sequence may not be recognized by regulatory proteins" in mammals other than mice is directly contrary to well known published experimental results that show that the WAP

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<sup>11</sup> See *In re Dinh-Nguyen*, 181USPQ 46, 48 (CCPA 1974).

<sup>12</sup> The success reflects the fact that deleterious integration is an infrequent event. The genomic DNA in all higher eukaryotes is composed very largely of intergenic, intronic and repeated DNAs. That is, so-called nonsense DNA. The "genes" are only a small proportion of the total DNA. The "critical" genes only a small proportion of the small proportion of total DNA made up by all the genes. Injected DNA integrates randomly into the genome. Integration into a critical gene therefore is highly unlikely. It is not a barrier to making and using transgenic mammals.

promoter generally is useful for expressing proteins the milk of transgenic mammals.

For instance, Puhler (1993), in reviewing work on the expression of foreign proteins in the milk of transgenic animals, points out that the WAP promoter has been reported to express hGH in rabbit, to express tPA in goat and mouse whey acidic protein and protein C in pig.<sup>13</sup> It also has been reported to express whey acidic protein, tPA, CD4, hGH, PS2 and protein C, in mouse.<sup>14</sup>

The expression obtained in experiments using heterologous genes, as summarized in Puhler, *supra*, generally ranged from .01 to 1.5 in microgram per milliliter (with one rather high result of 410) in mouse, was somewhat less than 3.7 in rabbit and was 3 in goat. The experimental results establish that the main transcription signals in the short murine WAP promoter function equivalently in mouse, rabbit and goat. Assertions to the contrary are not supported by any countervailing evidence. This ground of rejection therefore should be withdrawn.

Finally, the rejection alleges a deficiency of enablement on grounds that "RNases might degrade the RNA expression product or proteases may degraded [*sic*] the protein expression product of the protein C DNA sequences." The assertions are purely speculative. The results all show that protein C can be expressed in the

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<sup>13</sup> An excerpt from Puhler summarizing the results is attached hereto as EXHIBIT 5.

<sup>14</sup> The reference to protein is to work related in the '995 application by Velandar et al.

milk of mice and pigs. That the application is enabling in this respect is shown by the results in the disclosure, published results of Velandar (1992) and others and declaration evidence made of record in the '995 application.<sup>15</sup>

The results in mice and pigs reasonably predict the results that will be obtained in other mammals. The facts therefore do not support the asserted dangers of RNA and protein degradation. The rejection does not establish reasons, despite the experimental results, to doubt that the disclosure is enabling for mammals as claimed. Accordingly, this ground of rejection should be withdrawn.

3. ENABLEMENT EXTENDS TO THE SCOPE OF WAP/PROTEIN C CONSTRUCTS DISCLOSED AND CLAIMED

The rejection alleges that it would require undue experimentation for the skilled artisan to make transgenic mammals in accordance with the claimed invention other than by using the exact same WAP promoter and protein C DNAs set forth in the illustrative experimental examples in the application.

In supporting the allegation the rejection argues only that the art is "unpredictable." It is submitted that deeming the art unpredictable in this manner does not constitute setting forth reasons to doubt the objective truth of the assertion that the DNAs recited in the rejected claims are suitable for making and using transgenic animals as claimed. Merely asserting that the

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<sup>15</sup> Velandar (1992) is attached hereto as EXHIBIT 6. A copy of the declaration is attached as EXHIBIT 7.



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art is "unpredictable" is not a proper ground for rejection under Section 112 even if it were true.

In fact, those of skill in the art upon reading the present disclosure immediately will perceive a variety of embodiments of the DNAs of the claimed invention. Clearly one skilled in the art immediately will appreciate that any of the particularly disclosed embodiments could be altered by using different restriction enzymes, joining schemes, linkers and the like to create a convenient DNA construct for practicing the claimed invention. The claims properly embrace such trivial alterations.

Moreover, the WAP promoter fragment and the protein C sequence can be altered by well-known *in vitro* techniques for mutagenesis. The technique readily can be used, for instance, to introduce point mutations. Such point mutation include silent mutations which alter the DNA sequence but, because of codon degeneracy, do not change the encoded amino acid sequences. It is equally easy to introduce conservative amino acid substitutions which generally will not affect protein function. The same may be said for non-essential regions in protein C. These facts are known to all of skill in the art.

Basic principles of molecular biology reasonably predict that the overwhelming majority, if not all, of DNAs of the claimed invention having silent mutations in the protein C-coding region will function the same as the exemplified DNAs in transgenic animals. The same can be said of DNAs which contain alterations that result in conservative amino acid substitutions in the encoded protein C. Furthermore, larger alterations can be

introduced without undue experimentation which, predictably, would provide an active protein C in accordance with the claimed invention. The claims properly embrace these trivial variations as well.

In addition, protein C is a well studied protein. The amino acid sequence of human protein C is publicly available. Genomic and cDNA sequences also are publicly known. Functional domains in the protein have been characterized and identified in the sequences. Mutant forms of the protein have been made and characterized and, indeed, have been patented. It is well within the level of skill to make and use DNAs encoding altered protein C polypeptides based on this information. It will not require undue experimentation to practice the claimed invention using DNAs encoding such polypeptides.

The basic principles of protein structure and function will be the same for protein C expressed in the milk of transgenic animals as in any other context. Indeed, it would a major scientific surprise if any protein expressed in transgenic milk did not behave according to well known principles. In light of the present disclosure, which shows that active protein C can be expressed with surprising efficiency by the claimed DNAs in transgenic animals, basic science provides a solid basis to assert that many protein C active polypeptides can be expressed in the same way. In fact, basic principles dictate this conclusion.

Therefore, It is respectfully submitted that the claimed invention properly embraces protein C encoding DNAs as claimed. The assertion that such DNAs are not

enabled is not supported by any reasons or evidence contrary to the foregoing statements of fact. Thus, it is urged that the rejection should be withdrawn.

4. THE APPLICATION DISCLOSES SEVERAL ASSAYS OF PROTEIN C ACTIVITY

The rejection states that "[A]pplicant has not taught an assay method to determine DNA sequences which encode a protein having protein C activity." This statement is incorrect. The specification sets forth several well known protein C activity assays such as those in EXAMPLES 7 and 8. Those of skill readily will appreciate how to use these assays to test protein C for activity, from transgenic milk as well as any other source.

Furthermore, it is noted that applicants are urged by the Patent Office not to belabor that which is known to those of skill in the art by repeating it in a disclosure.<sup>16</sup> The claimed invention relates to specific transgenic mammals which express protein C by a specific genus of DNAs. Methods for assaying protein C activity, inter alia, are well known and may be employed in the conventional manner in carrying out the invention. Thus, it is respectfully submitted that the application by definition is enabling for assays of protein C activity because they are well known in the art.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The meaning of "substantially" and "variant thereof" is set forth with respect to the 5' 4.2kb WAP

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<sup>16</sup> *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

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promoter fragment on page 20 line 2 through page 21 line 2, for instance.

Substantially similar genomic protein C fragments are defined on page 18 lines 5-24, for instance. The passages reasonably will inform those of skill in the art of the metes and bounds of the claimed invention to the maximum extent permitted by the art.

It is submitted that the claims are definite and comply with the requirements of Section 112, second paragraph.

**FIRST REJECTION UNDER 35 U.S.C. §103**

All of the claims, except claim 11, have been rejected for obviousness over Pittius et al. ("Pittius"), Grinnell et al. ("Grinnell"), Brinster et al. ("Brinster") Campbell et al. ("Campbell") and Clark et al. ("Clark").

The references and the differences between the prior art and the claimed invention are discussed in detail below, especially in section II. Briefly, Grinnell (1987) is cited as teaching the expression of human protein C in tissue culture cells. Pittius is cited for teaching the expression of human t-PA in the milk of a transgenic mouse using a mouse whey acidic protein gene. Brinster is cited for teaching that "intron sequences enhance[s] the expression of a transgene in transgenic mice." Campbell is cited for teaching the sequence of a mouse whey acidic protein gene. Clark is cited for teaching that compounds of pharmaceutical interest can be produced in the milk of transgenic animals.

The rejection asserts that the claimed invention would have been obvious because "the ordinary artisan would be provided a reasonable expectation of success in producing protein C or any other protein of interest in the milk of a transgenic non-human mammal." The rejection particularly alleges that this would be so "where the transgene is composed of the genomic sequence for protein C or a protein of interest operatively linked to the mouse whey acidic promoter."

More specifically the rejection alleges that the "The 4.2kb Sau3A-Kpn1 fragment of the whey acidic promoter" recited in the claims would have been "[o]bvious over the smaller fragment taught by Pittius" on grounds that "[optimizing] expression would be within the scope of skills of the ordinary artisan."

In addition, the rejection alleges that "[T]he specific genomic protein C DNA sequence would be a matter of choice on the part of the inventor [sic]."

The rejection is traversed for the reasons set forth below. First, in Section I, the rejection is traversed because (1) it does not set forth any reason the specific DNAs recited in the claimed invention would have been obvious and, even more important, because (2) the rejection does not refer to or address the unexpected results achieved by the claimed invention or set forth any reasons ever purporting to show that the claimed invention would have been obvious even though it achieves these results.

The rejection also is traversed, in Section II, as failing to set out a proper *prima facie* case that it would have been obvious to those of ordinary skill in the art to express active protein C in the milk of a transgenic animal, even if the claimed invention did not recite particular DNAs or did not achieve unexpected results which establish patentability.

**I. THE CLAIMED INVENTION ACHIEVES "UNEXPECTED RESULTS" AND WOULD NOT HAVE BEEN OBVIOUS TO THOSE OF ORDINARY SKILL IN THE ART**

**1. THE REFERENCES NEITHER TEACH NOR SUGGEST THE DNAs RECITED IN THE REJECTED CLAIMS AND THE REJECTION THEREFORE DOES NOT SET OUT PROPER GROUNDS FOR PRIMA FACIE REJECTION**

The claimed invention, as set forth above, is directed to transgenic mammals containing specific WAP promoter/protein C DNAs. The prior art does not teach or suggest DNAs in accordance with the claimed invention.

The rejection alleges that the 4.2 kb WAP promoter fragment specifically recited in the claimed invention would have been obvious over "[T]he smaller fragment taught by Pittius, as the optimization of expression would be within the scope of the ordinary artisan." The rejection furthermore asserts that "[T]he specific genomic protein C DNA sequence would be a matter or choice on the part of the inventor [sic]."

These assertions do not establish grounds for rejection under Section 103. There is nothing in the prior art which suggests "optimization" of the sort implied by the rejection. Furthermore, there is nothing in the prior art to justify the assertion that the

"genomic protein C DNA sequence" specifically recited in the claims was chosen arbitrarily and therefore would have been obvious to those of ordinary skill in the art.

It is a principle of patent practice that a product and its properties are one and the same. Unobviousness of the properties establish unobviousness of a product. The transgenic animals of the claimed invention have unexpected properties of improved expression of protein C in milk and greater tissue specificity of expression. These properties are set out in the disclosure. Yet, the rejection does not address the unexpected properties of the claimed invention. The rejection therefore does not establish grounds for a *prima facie* obviousness rejection and should be withdrawn.

2. THE PRIOR ART WOULD NOT HAVE PROVIDED THE  
MOTIVATION TO EXPRESS PROTEIN C IN TRANSGENIC  
MAMMALS CONTAINING THE SPECIFIC DNAS OF THE  
CLAIMED INVENTION

The rejection asserts that the long WAP promoter of the claimed invention would have been obvious by mere "optimization" and the genomic protein C-encoding DNA or the claimed invention would have been obvious as a "choice." It is respectfully submitted that the prior art does not support either assertion.

The record does not provide evidence that those of skill in the art would have been motivated to perform any experiment that, allegedly, would have rendered obvious the long WAP promoter fragment recited in the claims. The rejection provides no indication of prior art in which such optimization experiments are carried out.

By the same token, the prior art does not support the assertion that a transgenic animal containing the claimed genomic protein C-encoding fragment would have been obvious.

The prior art relating to transgenic animals relates only the short WAP promoter and neither teaches nor suggests any long WAP promoter, let alone the long WAP promoter of the claimed invention. No benefits of a long WAP promoter are suggested in the prior art nor is there a suggestion to undertake "optimization" experiments to investigate, in a purely speculative endeavor, if longer or shorter fragments of the WAP promoter might give improved results.

The same is true for the assertion regarding the protein C-encoding genomic fragment of the claimed invention. The prior art reports and suggests using cDNAs, for the most part. Whatever suggestions there may have been to use genomic fragments is indistinct and would not have rendered obvious the protein-C encoding fragments of the claimed invention, which are recited with particularity.

3. THE REJECTION IS BASED ON IMPERMISSIBLE HINDSIGHT RECONSTRUCTION

Only the present application discloses transgenic animals that express protein C in their milk and contain the particularly recited DNAs of the claimed invention. The prior art is void of any mention of either the 4.2 kb WAP promoter fragment or the genomic protein C-encoding DNA recited in the claims. The assertion that the claimed



invention would have been obvious thus is possible only on the basis of impermissible hindsight reconstruction.<sup>17</sup>

4. THOSE OF ORDINARY SKILL IN THE ART WOULD NOT HAVE HAD A REASONABLE EXPECTATION THAT THE CLAIMED TRANSGENIC ANIMALS WOULD EXPRESS ACTIVE PROTEIN C BETTER THAN OTHER TRANSGENIC ANIMALS

As set forth in the disclosure in EXAMPLE 11, transgenic animals of the claimed invention express surprisingly more protein C in their milk than animals in which protein C expression is promoted by the 2.4 kb WAP promoter of the prior art.

As set forth on page 48, lines 11-15 and in Table 5 on page 49 of the present disclosure, for instance, protein C was expressed in the milk of animals of the claimed invention in concentrations between 140 and 4,000 micrograms per milliliter. These concentrations are much higher than the results previously achieved using the 2.4 kb short WAP promoter fragment and a cDNA encoding protein C. For instance, as stated on page 33, lines 26-28, the majority of mice produced by microinjection of WAPpC1 produced protein C in milk in concentrations ranging between 1 and 4 micrograms per milliliter.

Production of protein C in 30 to 1,000-fold higher concentrations than previously observed was entirely unexpected. There was no basis upon which those of ordinary skill in the art could have expected such high levels of expression. There is no basis to make a rejection for obviousness over these unexpected results.

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<sup>17</sup> *Grain Processing Corp. v. American Maize Products Corp.*, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988).

The rejection does not properly address the claimed invention in this regard. The prior art does not suggest that transgenic animals containing the DNAs specifically recited in the claims would be any different than transgenic animals containing any other WAP/protein C-encoding DNAs. Whatever motivation might have been present, those of ordinary skill in the art could not have had a reasonable expectation that the DNAs recited in the claimed invention would be better than any other DNAs for expressing protein C in the milk of transgenic animals. That is, they could not have had a reasonable expectation of success in this regard.

Thus, insofar as the goal of "optimization" would have been increased expression of protein C in milk, those of ordinary skill in the art could not have had a reasonable expectation of success that transgenic animals containing the particularly recited DNAs of the claimed invention would have been any better than all the DNAs which are not encompassed by the claimed invention.

Selection is the essence of invention. The claims are not directed to transgenic animals containing any WAP promoter fragment. Rather they are directed to transgenic animals that contain specifically defined WAP promoter fragments.

The rejection is improper for failing to show that those of ordinary skill in the art would have had a reasonable expectation that transgenic animals containing the specifically recited DNAs comprising "substantially the 5' 4.2 kb Sau3A - Kpn1 promoter of the mouse whey acidic protein gene or a variant thereof" for expressing

a polypeptide having protein C activity would be successful for expressing protein C any better than a myriad of other fragments that also might have been tried.<sup>18</sup>

5. THE CLAIMED INVENTION ACHIEVES ENTIRELY UNEXPECTED RESULTS

Unobviousness of a product is not simply a matter of structural obviousness but depends on the properties of the product as well.

The rejection alleges variously that the claimed transgenic animals would have been obvious because it would have been obvious to those of ordinary skill to optimize expression and because using the genomic DNA for protein C would have been a matter of choice.

As set forth above, the results obtained by the transgenic animals of the claimed invention are unexpected. These unexpected results obviate the asserted obviousness of the invention, notwithstanding the foregoing remarks concerning other aspects of the rejection.

EXAMPLE 11 clearly states that transgenic animals in accordance with the invention expressed surprisingly high concentrations of protein C in their milk, which dramatically exceeded the results achieved with transgenic animals using other DNAs.

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<sup>18</sup> Indeed, if the art is as unpredictable as the rejection repeatedly states, than those of skill in the art could not have had a reasonable expectation of success that the claimed DNAs would work at all!

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The concentrations of protein C in the milk of transgenic animals of the claimed invention measured by binding to a monoclonal antibody is described on page 48, lines 4-11 of the disclosure as "[A]t least 40 fold more than the concentration of protein C observed in other transgenic mice."

The following paragraph, on lines 11-15 on the same page, points out that protein C, measured by binding to a polyclonal antibody, was present in the milk of these animals at concentrations between 140 and 4,000 micrograms per milliliter, "Exceeding even more dramatically the concentration attained with the 2.4 kb 5' WAP promoter...."

At page 48, lines 25-30, the disclosure points out that "The high concentration of protein C allowed the amidolytic activity [of protein C produced by the transgenic animals] to be assayed directly in whey. This contrasted sharply with the necessity to use a capture method to concentrate protein C ... from mice transgenic for the 2.4 WAP promoter fragment."

In addition, on page 49 lines 20-31 and extending onto page 50, the application discloses that, "[H]istological examination showed that at least 99% of the protein C expression occurred in the mammary glands in these animals. These results contrast with the results achieved using the whey acidic protein promoter constructs that contained only the 2.4 kb promoter fragment."

As summarized on page 50, lines 2-5, the claimed invention provides higher levels of expression and greater

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tissue specificity of expression than could have been expected.

It is respectfully submitted that the claims do not recite transgenic animals which contain DNAs of an entirely arbitrary character, as the rejection alleges. The disclosure very clearly lays out unexpected results attained by the claimed invention which obviate any such assertion. Any rejection for obviousness which rests on such an assertion improperly ignores these results.

In short, the present rejection for obviousness does not set forth valid grounds for rejection under Section 103 because it does not establish "motivation" or "reasonable expectation of success," because it is based on impermissible hindsight reconstruction and because it ignores the dispositive unexpected properties of the transgenic animals of the claimed invention.

**II. THE EXPRESSION OF ACTIVE PROTEIN C IN THE MILK OF TRANSGENIC ANIMALS WOULD NOT, IN ANY CASE, HAVE BEEN PRIMA FACIE OBVIOUS**

Protein C is a complex protein that undergoes a variety of unusual modifications as set forth in the background section of the application, for instance. The prior art did not teach or suggest that mammary epithelial cells *in vivo* would be a good prospect for carrying out these modifications efficiently, including modifications necessary for protein C activity.

To the contrary, the prior art suggested that other cells would be better for transgenic expression. A proper interpretation of the prior art as a whole shows that those of ordinary skill would NOT have been motivated

to express protein C in milk in a transgenic animal. It shows, furthermore, that they would not have had a reasonable expectation of success in attempting to express protein C this way. And it shows, moreover, that the prior art teaches away from the claimed invention rather than suggesting it, strongly demonstrates patentability.<sup>19</sup>

1. Pittius does not provide probative information that active protein C can be expressed in similar fashion because the requirements for expressing t-PA are different from those for protein C

Pittius relates to t-PA, a relatively simple protein compared to protein C. Therefore, even assuming *arguendo* that the t-PA expression demonstrated by Pittius could be considered probative of the expression of some other proteins in transgenic milk, Pittius in no way is probative of active protein C expression.

The post-translational modifications that occur naturally in the two proteins and the natural effect of the modifications on activity show that t-PA expression would not have rendered obvious the expression of active protein C.

For instance, t-PA is processed naturally in cells by proteolytic cleavage which produces an enzymatically active protein. Protein C is secreted in an inactive, zymogen form. Furthermore, the proteases that carry out the processing are not the same for the two proteins. Likewise, although both proteins are glycosylated, the

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<sup>19</sup> *Gillette Co. V. S.C. Johnson & Co.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990).

patterns of glycosylation are very different and are carried out by different enzymes. Proper processing of t-PA in a cell does not indicate that protein C will be processed correctly, even for the same types of modification.

Even more important, protein C undergoes two additional covalent modifications which are not observed in t-PA at all. The first,  $\beta$ -hydroxylation, is relatively rare in proteins. The second, gamma carboxylation, generally is rare in proteins but is characteristic in the vitamin K-dependent enzymes of the coagulation cascade.<sup>20</sup> Protein C must be gamma carboxylated to exhibit anti-coagulant activity. Gamma carboxylation is not found in t-PA. The activity of t-PA does not depend on or reflect this modification at all. The expression of t-PA in mammary cells does not provide an iota of information about the ability of the cells to gamma carboxylate protein C. It provides even less information that the degree of carboxylation would be enough for activity.

In fact, the cellular machinery necessary for gamma-carboxylation is not present in most cells. As a consequence, for instance, anti-coagulant active protein C cannot be expressed in *E. coli*. In contrast, active t-PA can be expressed in *E. coli*. Protein C also cannot be expressed efficiently in an active form by most eukaryotic cells, which cannot efficiently gamma carboxylate any protein, let alone an over-expressed foreign protein. Again, in contrast, active t-PA can be expressed in most eukaryotic cells.

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Gamma carboxylation is not a glycosylation.

Thus, the expression of t-PA in the milk of transgenic animals does not in the least suggest that active protein C can be expressed in the same way. Accordingly, Pittius (1987), which is directed solely to the expression of the non-carboxylated protein t-PA, does not indicate that the present invention would have been obvious, and it is respectfully urged that any rejection based on Pittius should be withdrawn.

Finally, it is reiterated that gamma-carboxylation is only one of several post-translation modifications that differ in protein C and t-PA. For instance, the proteolytic processing of the protein C precursor protein into mature two-chain protein C is quite different from the processing of t-PA precursor into mature t-PA. Little was known about the enzymes that carried out several of the cleavages in these pathways, and processing of t-PA in epithelial cells or milk in a transgenic animal would not have been probative that protein C also would be correctly processed.

In addition, protein C is uniquely  $\beta$ -hydroxylated, whereas this modification does not occur at all in t-PA. Furthermore, protein C is glycosylated differently from t-PA and the glycosylation is done by different enzymes, which are present in different cells. Thus, it would not have been obvious that active protein C could be made efficiently in mammary epithelial cells, simply because some expression had been achieved for t-PA.

And, it should be noted that the stability of protein C to proteases in mammary epithelial cells or milk could not have been inferred from the t-PA experiments.



For instance, t-PA was cleaved inappropriately by proteolytic enzymes in transgenic milk, presenting something of a problem for t-PA production. Furthermore, quite unexpectedly, it was found that plasmin was among the proteases that act on t-PA in transgenic milk. The degradation of t-PA by these proteases at least would have indicated that protein C in transgenic milk would be deleteriously affected by proteases.

2. THE PRIOR ART SHOWED THAT CULTURED MAMMARY EPITHELIAL CELLS DO NOT EFFICIENTLY GAMMA CARBOXYLATE PROTEIN C, TEACHING AWAY FROM EXPRESSION OF PROTEIN C IN TRANSGENIC MILK

Grinnel (1987) interpreted in light of the relevant art as a whole shows that the present invention would not have been obvious.

First, it is respectfully submitted that Grinnel (1987) would not have been considered probative that active protein C could be expressed in the milk of a transgenic animal, because the report relates to protein C expression in kidney cells in culture. Furthermore, several other publications related that the best expression of protein C in culture occurred in kidney cells, not mammary epithelial cells.<sup>21</sup> Indeed, the worst results in terms of the rates of synthesis and secretion of active protein C were obtained in a mouse mammary epithelial cell line.

Moreover, studies of the ability of cells in whole organs to carboxylate proteins showed that liver cells

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<sup>21</sup> Work on the production of protein C in cell culture is reviewed in Grinnel (1990), submitted as document B2 in the I.D.S. submitted on December 31, 1992.

were the most active of the tissues tested. Thus, not only had mammary gland epithelial cells been shown to be relatively poor producers of protein C and kidney cells to produce fully gamma carboxylated protein C more efficiently than other cells in culture, but the same relative efficiencies had been shown *in vivo* where kidney cells had been shown to have the highest capacity to gamma carboxylate proteins. Accordingly, (1) mammary epithelial cells would not have been the cell-type of choice for expressing protein C *in vivo* and (2) it would not have been expected that protein C could be expressed efficiently in the milk of any mammal, since mammary epithelial cells in culture had been shown to produce only small amounts of protein C, which in any event was largely inactive.

Indeed, Grinnel and co-workers in Yan (1989) and Grinnel (1990) set forth objective criteria for determining whether a host cell might be useful to express protein C in useful amounts.<sup>22</sup> Yan (1989) indicates that cells useful in this regard must produce at least 10 pg of protein C/cell/day. Grinnel (1990) indicates that the cells should secrete at least 10  $\mu$ g of protein C/ml/day into the culture medium. Evaluating the available reports on protein C expression in culture and *in situ* by the Yan and Grinnel criteria indicates clearly that kidney cells would have been the best choice for protein C production and mammary epithelia cells would have been the worst choice. Thus, Grinnel (1987), which relates best to kidney cell expression, actually indicates that it would

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<sup>22</sup> As mentioned above, Grinnel (1990) is document B2 in the I.D.S. submitted on December 31, 1992. A copy of Yan (1989) is attached hereto as EXHIBIT 8.

not have been obvious to express high levels of protein C in the milk of a transgenic animal, as disclosed and claimed in the present application.

A more detailed examination of the references further supports this conclusion. Grinnel (1987) reported that protein C was expressed efficiently in a human kidney cell line transfected with a vector for expressing human protein C. The average rate of protein C production in the cells was about 10 pg/cell/day and about 10 µg/ml/day of protein C was secreted into the culture medium. The protein C produced by the cells was gamma carboxylated and it was active.

Grinnel and co-workers published several additional reports further relating their work to express protein C in cell culture, most successfully in the 293 kidney cell line. The best results consistently were obtained using kidney and liver cell lines, as summarized in Grinnel (1990).

These results are further emphasized in Berg (1991).<sup>23</sup> It will be readily apparent from the article that Grinnell and co-workers viewed efficient gamma carboxylation as key to efficient expression of protein C on any cell. This was so much the case they endeavored to increase the activity of gamma carboxylase by infecting the cells with adenovirus.

As to mammary gland cells, Suttie (1986) and Oppenheimer et al. specifically reported that C127 mouse

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<sup>23</sup>

A copy of Berg is attached hereto as EXHIBIT 9.

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mammary epithelial cells in culture expressed little active protein C (reviewed in Yan (1989)<sup>24</sup>. Suttie reported that less than 1 pg/cell/day (assuming 10<sup>6</sup> cell/ml) of protein C was expressed, and even this was 60% to 70% inactive in an anti-coagulation assay. (Related in Yan (1989). Thus, the results using mammary epithelial cells in culture clearly indicated that mammary glands could not express high levels of active protein C.

Finally, at least as to the relative efficiency of liver and kidney cells to produce active protein C (since mammary tissue wasn't tested), the *in vitro* results agree with studies by Buchtel (1983) and by Vermeer (1982) on the distribution of protein carboxylation in the tissues of animals, which showed the highest levels of carboxylation in cells of the liver.<sup>25</sup>

Thus, (1) only kidney and liver cells had been shown to offer promise for efficient gamma carboxylation consistent with the production of viable quantities of protein C and (2) it had been found that mammary cells did not efficiently modify protein C and appeared not to be promising for producing the protein in anti-coagulant active form.

Accordingly, the prior art directed the skilled artisan to produce protein C in kidney or liver cells, and

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<sup>24</sup> A copy of Suttie (1986) is attached hereto as EXHIBIT 10.

<sup>25</sup> A copy of Buchtel (1983) is attached hereto as EXHIBIT 11. A copy of Vermeer (1982) is attached hereto as EXHIBIT 12.

further directed the skilled artisan not to produce protein C in mammary cells.

Even if it is maintained that the prior art provided a suggestion regarding the production of active protein C in a transgenic animal, therefore, it cannot be maintained that it would have been obvious to express the protein in mammary epithelial cells for secretion into milk.

3. BRINSTER DOES NOT TEACH OR SUGGEST THAT ALL INTRONS INCREASE EXPRESSION IN TRANSGENIC ANIMALS

The rejection alleges that Brinster teaches that introns will increase the expression of genes in transgenic animals. This is not the case. Brinster teaches, at most, that some introns can increase expression in transgenic animals. Brinster clearly recognizes that the phenomena is unpredictable. Brinster does not provide any real guidance in this regard. It is not clear that the reference even rises to the level of an invitation to try.

Moreover, the prior art is ambiguous on the effects of genomic DNA verses cDNA in this regard. Almost all the genes discussed above concerning transgenic expression using a WAP promoter were cDNAs, not genomic DNAs. Of the two genomic DNAs reported in this context, hGH was expressed while PS2 was not expressed.<sup>26</sup> Thus, the overall results with genomic DNAs had not been as good as those with cDNAs, which certainly would weigh against any attempt to use genomic DNAs to express protein C.

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See Tomasetta (1989) attached hereto as EXHIBIT 13.

4. CLARK DOES NOT PROVIDE THE NECESSARY  
MOTIVATION PROPERLY TO COMBINE THE  
REFERENCES TO REJECT THE CLAIMS AS BEING,  
PRIMA FACIE, OBVIOUS OVER THE CITED  
REFERENCES

Clark is cited as providing "motivation" to combine the teachings of Grinnell and Pittius, i.e., it is alleged, *inter alia*, that one of ordinary skill would have been motivated to express protein C per Grinnell in transgenic animals following Pittius, for the benefits expressed by Clark.

This rationale is legally incorrect. A desirable goal of a general nature, such as efficiently producing pharmaceutically important proteins, does not provide the motivation necessary to properly reject, as being obvious under §103, claims directed to a specific means for achieving that goal, such as the transgenic animals of the claimed invention for producing protein C.

Clark merely reviews the possibility to express proteins in transgenic animals. Clark certainly is not directed specifically to transgenic expression of human protein C or to any transgenic animal of the claimed invention. Clark points out many difficulties that could prevent the expression of any protein in transgenic milk, referring specifically to possible limitations of mammary gland cells properly to carry out necessary post-translational modifications and the ubiquitous danger that a transgenic protein will be degraded by the proteases in milk.

Thus, notwithstanding Clark's general optimism regarding transgenic protein production, taken alone or together with the other prior art cited in the present

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rejection, the reference would not have provided one of ordinary skill in the art with the requisite motivation or the reasonable expectation of success to support a rejection on obviousness grounds. Accordingly, it is respectfully urged that the rejection is improper and should be withdrawn.

For the foregoing reasons it is respectfully submitted that the rejection of claims 1-10 and 12-15 for obviousness be withdrawn.

**SECOND REJECTION UNDER 35 U.S.C. §103**

Claim 11 has been rejected for obviousness over Colpan et al. ("Colpan") in view of Hogan et al. ("Hogan"). Colpan is cited for teaching purification of DNA by anion exchange HPLC. Hogan is cited for teaching that DNA for making transgenics should be free of contaminants that would deleteriously affect normal embryo development.

The rejection assert that "New uses for known methods do not necessarily overcome the art in the absence of unexpected results." On this basis the rejection requires "[S]ide by side comparisons" which show unexpected results to prove that the invention would not have been obvious. The rejection is traversed for the reasons set forth below.

It is respectfully submitted that the rejection does not set out a proper case of *prima facie* obviousness. It implies that purification of DNA according to Colpan was a "known method" and it asserts that Hogan teaches the importance of removing deleterious contaminants from DNA

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used to make transgenic mice. The rejection does not set out a reasoned argument showing that a person of ordinary skill would have been motivated to use the Colpan method to make transgenic DNA. The rejection does not set out a reasoned argument to establish that a reasonable expectation of success would have attended such an endeavor. And the rejection does not address the fact that Hogan, which was published after Colpan, only teaches other methods for purifying DNA to make transgenic mice.

In fact, the references cited by the examiner indicate that the claimed invention would NOT have been obvious. As noted in the rejection, Hogan teaches that deleterious impurities must be removed from DNA for making transgenic animals. However, Hogan also teaches what it considers the best purification methods for this purpose. Hogan, written in view of Colpan, does not teach or suggest that a method according to Colpan would be useful in this regard. Hogan directs those of ordinary skill exclusively to methods other than the method in Colpan.

Hogan is an authoritative laboratory manual of reliable techniques for making transgenic mice. It indicates that those of ordinary skill in the art would not have used a method according to Colpan. In this regard, Hogan teaches against the claimed invention.

Colpan does not remedy this deficiency in Hogan as a reference under Section 103. Colpan neither teaches nor suggests using DNA purified by anion exchange HPLC to make transgenic animals.



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It is respectfully suggested that all purification methods suffer from imperfections. Those of ordinary skill in the art would not resort to the method in Colpan, as opposed to those taught by Hogan specifically for purifying DNA to make transgenic animals, without a motivation to do so. New methods pose risks. Colpan at most is an invitation to try anion exchange HPLC purified DNA in making transgenic animals. Nothing in the prior art suggested that the method would be successful in this regard or superior to the methods in Hogan.

The rejection does not address either point. It does not establish that those of ordinary skill in the art would have been motivated to forego the reliable methods in Hogan to use an untried method as set forth in Colpan. Furthermore, the rejection does not establish that they would have had a reasonable expectation that anion exchange HPLC would be as effective at removing deleterious contaminants as the methods in Hogan, whatever the asserted purity by weight or mass of DNA prepared by the method.

Finally, it should be noted that claim 11 is directed to making transgenic animals using the particular WAP promoter and protein C-encoding DNAs discussed above. The rejection does not address this aspect of the claimed invention, which distinguishes the claimed method over Colpan and Hogan, notwithstanding the foregoing remarks.

Accordingly, for the reasons set forth above, it is respectfully submitted that the rejection is improper and should be withdrawn.

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In view of the foregoing amendments and remarks it is believed that the application now is in condition for allowance, and favorable disposition of the application is solicited.

**A FINAL NOTE**

Documentation provided in this response reflects applicants' assessment that those of skill in the art will appreciate the veracity of the foregoing remarks concerning the level of skill, routine techniques and basic principles of science in this art, *inter alia*. It is believed that an examiner will be in the same position as those of skill in the art, in this respect, as well. Should the examiner desire additional documentation in this regard, it will be provided upon request.

Applicant specifically reserves the right, however, to submit additional documentation supporting the foregoing remarks if applicable grounds of rejection are reinstated in future Office Actions. Applicant particularly reserves the right to make of record additional documentation to complete the record in this regard in the event rejections are appealed to the Patent and Trademark Office Board of Appeals and Patent Interferences.

January 24, 1994  
Date

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